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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/760,119	01/12/2001	Sarah S. Bacus	MBHB01-034	1978

20306 7590 12/01/2004

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 12/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/760,119	BACUS, SARAH S.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-6 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-6 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 2/17/2004.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Sections of Title 35, U.S. code not found in this Office action can be found in a previous action.

2. Claims 1-6 are pending. After review and reconsideration of the instant claims in light of the prior art, the claims will be examined to the extent that they read on the species of "terminal differentiation" and "apoptosis".

3. Claims 1, 2, 5 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bacus (U.S. 5,288,477, cited in the previous Office action) in view of the abstract of Smith and al-Mounhri (Biomed Pharmacother, 1998, Vol. 52, pp. 116-121) and any of Porter (US 5,498,522) or Los et al (US 6,447,997) or Barbera-Guillem et al (US 5,536,642).

Claim 1 is drawn to a method for determining a response to administration of a chemotherapeutic or chemopreventative agent comprising collecting a first tissue or cell sample from an individual before exposing the individual to the chemotherapeutic or chemopreventative agent; collecting a second tissue or cell sample from the individual after exposing the individual to the chemotherapeutic or chemopreventative agent; immunohistochemically staining the first and the second tissue or cell samples using a detectably labeled antibody directed against a biological marker associated with terminal differentiation; measuring the optical density of the stained cells of step (c) wherein the stained cells are illuminated with light having a wavelength absorbed by the stain; determining whether expression of the biological marker associated with apoptosis was increased following exposure to the chemotherapeutic or chemopreventative agent. Claim 2 embodies the method of claim 1 wherein the detectable label is a chromogen or fluoraphore. Claim 5 embodies the method of claim 1 wherein the optical density of the stained cells is preformed by image analysis. Claim 6 embodies the method of claim 5 wherein the image analysis is preformed by splitting a signal comprising the optical density of the stained cells into a multiplicity of signals that are processed using optical filters having different absorption and transmittance properties, so that each signal is specific for one of a multiplicity of stains used to stain the cells.

Bacus ('477) teaches a method for determining the effectiveness of a therapeutic agent in the treatment of cancer by measurement the ability of the therapeutic agent to induce terminal differentiation wherein malignant cells of the cancer over express an oncogene product comprising obtaining from a human having cancer a biopsy comprising viable malignant cells; dividing said biopsy into a first and a second portion; treating the first portion with a compound having specific binding affinity for said oncogene product; maintaining said first and second portions in physiologically acceptable medium for an amount of time sufficient to induce maturation in the viable malignant cells of the first portion; and comparing the percentage of cells in the first portion which exhibit markers of terminal differentiation with the percentage of cells in the second portion which exhibit markers of terminal differentiation, wherein the effectiveness of treatment correlated with the degree of terminal cell differentiation, or alternatively comparing the amount of oncogene product in said first portion with the amount of a oncogene product in said second portion (claims 1 and 10). Bacus teaches that cell proliferation is yet another measure of the extent of terminal cell differentiation, and that a stabilization and reduction of cell populations as compared to untreated control cells indicates substantial terminal differentiation (column 11, lines 53-61). Bacus teaches that induction of a translocation of the Her-2/neu receptor from the cell surface to the cytoplasm or perinuclear region of the cell induce a terminally differentiated phenotype in the tissue or cell sample is indicative of terminal differentiation and that this induction can be expedited by means of binding by antibodies (claims 4-6 and 11-17 and column 5, lines 1-38). Bacus teaches that normal cells are devoid of Her-2/neu on the surface membrane (column 4, lines 62-68). Bacus teaches the anti-Her-2/neu antibody conjugated to a fluorescent dye and indirect methods of antibody detection such as the use of peroxidase-anti-peroxidase staining or alkaline phosphatase staining, thus fulfilling the specific embodiment of claim 2. Bacus teaches that membrane bound Her-2/neu may be quantified by digitized image analysis in conjunction with fixation and staining procedures (column 11, lines 6-25). Bacus teaches that cell sample can be stained with an anti-Her-2 antibody and an additional DNA stain and that digitization of two filtered images of the single sample, one for each specific stain allows for the summation of the optical density value for the DNA stain and the optical density value for the Her-2/neu stain (column 10, lines

20-65), thus fulfilling the specific embodiments of claim 6. Bacus does not teach obtaining a biopsy sample before and after treatment with the therapeutic agent.

The abstract of Smith and al-Mounhri teaches that neoadjuvant chemotherapy is a rapidly evolving area in the management of early operable breast cancer, achieving significant response I around 80% of patients with the concomitant reduction in the necessity of mastectomy. The abstract further teaches that neoadjuvant chemotherapy allows for serial biological measurements of treated breast cancers, which in turn, may aid in the selection of appropriate treatment for individual patients and allow the rapid assessment of new therapies. Any of Porter or Los et al or Barbera-Guillem et al teach the monitoring of therapeutic effectiveness of chemotherapy in a mammal comprising administering a therapeutic agent, performing a biopsy of the tumor and detecting the in vitro level of a marker in the tumor cells as indicative of clinical response to the therapeutic agent (see claims 23 and 34 of Porter; claim 1 of Los et al and claim 4 of Barbera-Guillem et al).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to determine the effectiveness of a therapeutic agent in the treatment of cancer by measurement the ability of the therapeutic agent to induce terminal differentiation by means of obtaining a sample of cells or tissues from said patient before administration of said therapeutic agent and obtaining a second sample of cells or tissues from said patient after administration of said therapeutic agent and quantitative the presence of Her-2/neu on the surface of cells from the pre-treatment group and the treatment group by means of an antibody labeled with a fluoraphore or a chromogen and quantitating the total number of cells by staining DNA, and subjecting the labeled cells to image analysis wherein the image analysis is performed by splitting a signal comprising the optical density of the stained biological sample into at least two signals that are processed using optical filters having different absorption and transmittance properties so that a signal from the labeled antibody can be separated from a signal from the labeled DNA, so that a percentage of cells expressing both labeled antibody and labeled DNA can be quantified in order to measure the effectiveness of the combined therapy in the induction of apoptosis in breast cancer cells in patients having undergone therapy. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Bacus ('477) on the targeting of stabilization and a reduction of a

cell population by means of terminal differentiation in a method of treating breast cancer and the teachings of the abstract of Smith and al-Mounhri on the serial biological measurements of treated breast cancer in vivo to determine if the treatment was appropriate fro the individual patient supplemented with the teachings of any of Porter or Los et al or Barbera-Guillem et al on the in vivo monitoring of therapeutic efficacy by assaying a sample taken from a patient after administration of a therapeutic agent.

4. Claims 1-3, 5 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bacus (U.S. 5,288,477) in view of the abstract of Smith and al-Mounhri (Biomed Pharmacother, 1998, Vol. 52, pp. 116-121) and any of Porter (US 5,498,522) or Los et al (US 6,447,997) or Barbera-Guillem et al (US 5,536,642) as applied to claims 1, 2, 5 and 6 above and in further view of the abstract of Vollmer et al (Cancer Research, 1992, Vol. 52, pp. 4642-4648) and the abstract of Dannecker et al (Ann Oncol, 1996, Vol. 7, pp. 391-395) and the abstract of Kopp et al (Cancer Research, 1995, Vol. 55, pp. 4512-4515).

Claim 3 embodies the method of claim 1 wherein the biological marker is p21, p27, p16, TGF-beta or SA-Beta-Gal.

Bacus ('477) teaches that terminal cell differentiation is determined by translocation of HER-2/neu from the cell surface membrane to the cytoplasm or perinuclear region of the cell and that translocation of HER-2/neu is determined immunohistochemically with an antibody which is specific for the HER-2/neu protein. Bacus does not teach terminal cell differentiation is determined by a detectably labeled antibody against TGF-beta.

The abstract of Vollmer et al (Cancer Research, 1992, Vol. 52, pp. 4642-4648) teaches that antiprogestins inhibit tumor growth by induction of terminal differentiation (last line). The abstract of Dannecker et al (Ann Oncol, 1996, Vol. 7, pp. 391-395) teaches that the antiproliferative action of an antiprogestin increased TGF-beta secretion by breast tumour cells (lines 14-18). One of skill in the art would reasonably conclude that the induction of terminal differentiation in breast tumor cells results in the secretion of TGF-beta by said cells. The abstract of Kopp et al (Cancer Research, 1995, Vol. 55, pp. 4512-4515) teaches that plasma levels of TGF-beta are increased in the first 2 to 6 weeks in breast cancer patients having undergone treatment with tamoxifen and experiencing remission. One of skill in the art would

reasonably conclude that the secretion of TGF-beta upon induction of terminal differentiation by antiprogestins would be measurable in the blood plasma of a patient

It would have been prima facie obvious at the time the claimed invention was made to measure the degree of terminal differentiation induced by the translocation of Her-2/neu translocation by measuring TGF-beta in the blood plasma before administration of the anti-Her-2/neu antibody and after the administration of the anti-Her-2 antibody. One of skill in the art would have been motivated to do so by the teachings of the abstracts of Vollmar et al and Dannecker et al which link the induction of terminal differentiation with TGF-beta secretion in breast tumor cells, and the abstract of Kopp et al which teaches that plasma levels of TGF-beta are markedly higher in breast cancer patients having undergone remission due to treatment. One of skill in the art would expect that breast cancer patients who undergo remission by the induction of terminal differentiation by administration of the anti-Her-2/neu antibody taught by Bacus would exhibit a marked increase in blood plasma levels of TGF-beta, because this was demonstrated for the therapeutic agent tamoxifen. One of skill in the art would conclude that the levels of TGF-beta secreted by breast cells are reflected in the level of TGF-beta in blood plasma.

5. Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bacus (U.S. 5,288,477) and the abstract of Smith and al-Mounhri (Biomed Pharmacother, 1998, Vol. 52, pp. 116-121) and any of Porter (US 5,498,522) or Los et al (US 6,447,997) or Barbera-Guillem et al (US 5,536,642) and the abstract of Vollmer et al (Cancer Research, 1992, Vol. 52, pp. 4642-4648) and the abstract of Dannecker et al (Ann.Oncol, 1996, Vol. 7, pp. 391-395) and the abstract of Kopp et al (Cancer Research, 1995, Vol. 55, pp. 4512-4515) as applied to claims 1-3, 5 and 6 above, and in further view of Dash et al (US 5,772,998).

Claim 4 embodies the method of claim 1 wherein the amount of biological marker protein is determined by ELISA. The combination of Bacus and the abstract of Smith and al-Mounhri, and any of Porter or Los et al or Barbera-Guillem et al, and the abstract of Vollmer et al and the abstract of Dannecker et al and the abstract of Kopp et al render obvious the instant claims with respect to the detection of TGF-beta in the blood plasma. None of the aforesaid references specifically teach the detection of TGF-beta by ELISA.

Dash et al teach a method for diagnosing a disease or disorder such as cancer comprising coating a first monoclonal antibody reactive with TGF-beta onto a surface, adding a sample containing an unknown amount of TGF-beta to a surface and adding a monoclonal or polyclonal antibody to react with the bound TGF-beta, and determining the presence of bound TGF-beta based on an enzymatic or colorimetric reaction (column 2, lines 37-48 and column 6, lines 39-54).

It would have been prima facie obvious at the time the claimed invention was made to measure TGF-beta in blood plasma by ELISA. One of skill in the art would have been motivated to do so by the teachings of Dash et al on the capture-ELISA method for quantitating the concentration of TGF-beta in a biological sample..

6. Claims 1-3, 5 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bacus (U.S. 5,288,477) and the abstract of Smith and al-Mounhri (Biomed Pharmacother, 1998, Vol. 52, pp. 116-121) and any of Porter (US 5,498,522) or Los et al (US 6,447,997) or Barbera-Guillem et al (US 5,536,642) as applied to claims 1, 2, 5 and 6, above, and in further view of the abstract of Warri et al (Journal of the National Cancer Institute, 1993, vol. 85, pp. 1412-1418, cited in a previous Offcie action) and Sasaki et al (Jpn J Cancer Research, 1998, Vol. 89, pp. 562-570) and the abstract of Srivastava et al (Anticancer Res, 1998, Vol. 18, pp. 4003-4010).

The combination of Bacus and the abstract of Smith and al-Mounhri and any of Porter or Los et al or Barbera-Guillem et al renders obvious the limitations of claims 1, 2, 5 and 6 for the reasons set forth above, with respect to the species of "terminal differentiation" as the biological marker as the anti-Her-2 antibody is directed against the Her-2 receptor which is associated with terminal differentiation as taught by Bacus. None of the aforesaid references teaches a biological marker associated with apoptosis, However, Bacus includes the stabilization and reduction of a cell population as part of the definition of terminal differentiation (column 11, lines 53-61). Said stabilization and reduction of a cell population can be achieved with apoptosis.

and

Warri et al teach that methods for treating breast cancer should target the induction of apoptosis to breast cancer cells (abstract, last sentence). Warri et al on the up regulation of

expression of TGF-beta after treatment with an anti-estrogen compound which causes apoptosis in breast cancer cells.

Sasaki et al teach an anti-ERBb2 antibody CH401 which inhibited tumor growth by the induction of apoptosis (page 568, first column, second full paragraph).

The abstract of Srivastava et al identifies TGF-beta and p21 as apoptotic genes in human breast cells.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to evaluate a patients response to chemotherapy comprising the administration of the anti-ERBb2 antibody, CH401, by means of obtaining a sample of cells or tissues from said patient before the treatment and obtaining a second sample of cells or tissues from said patient after treatment and quantitating the induction of apoptosis of said cells by means of an anti-p21 antibody or an anti-TGF-beta antibody labeled with a fluoraphore or a chromogen and quantitating the total number of cells by staining DNA, and subjecting the labeled cells to image analysis wherein the image analysis is performed by splitting a signal comprising the optical density of the stained biological sample into at least two signals that are processed using optical filters having different absorption and transmittance properties so that a signal from the labeled antibody can be separated from a signal from the labeled DNA, so that a percentage of cells expressing both labeled antibody and labeled DNA can be quantified in order to measure the effectiveness of anticancer therapy by measuring the induction of apoptosis in breast cancer cells in patients having undergone therapy. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of the abstract of Warri et al on the targeting of apoptosis to breast cancer cells as a therapeutic approach for treating breast cancer, the teachings of the Sasaki et al on the CH401 antibody which induces apoptosis in breast cancer cells expressing Her-2, the teachings of the abstract of Srivastava et al which identify TGF-beta and p21 as genes which are expressed during apoptosis of breast cells, and the teachings of Bacus on the targeting of stabilization and a reduction of a cell population in a method of treating breast cancer. One of skill in the art would be motivated to use the antibody of Sasaki et al because said antibody induced programmed cell death in cells expressing Her-2 and the induction of apoptosis would "stabilize and reduce the cell population" of a breast tumor by inducing apoptosis rather than terminal differentiation.

7. Claims 1-3, 5 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bacus (U.S. 5,288,477) and the abstract of Smith and al-Mounhri (Biomed Pharmacother, 1998, Vol. 52, pp. 116-121) and any of Porter (US 5,498,522) or Los et al (US 6,447,997) or Barbera-Guillem et al (US 5,536,642) as applied to claims 1, 2, 5 and 6, above, and in further view of the abstract of Gillett et al. (J Pathol. 1999 Jan;187(2):200-6), the abstract of Emig et al (Br J Cancer. 1998, Vol. 78, pp.1661-1668) .

Claim 3 is drawn in part to the method of claim 1 wherein the biological marker is p27 or p16.

Neither Bacus (U.S. 5,288,477), nor the abstract of Smith and al-Mounhri , nor any of Porter (US 5,498,522) or Los et al (US 6,447,997) or Barbera-Guillem et al teach p27 or p16 as a biological marker protein associated with terminal differentiation or apoptosis.

The abstract of Gillett et al. (J Pathol. 1999 Jan;187(2):200-6) teaches that low levels of p27 was observed in high grade, rapidly proliferating breast tumors.

The abstract of Emig et al (Br J Cancer. 1998, Vol. 78, pp.1661-1668) teaches antibodies to human p16 can be used in immunohistochemical analysis to monitor the expression of p16 in breast cancer cells and that breast cancer cells with high proliferative activity exhibit cytoplamic p16 accumulation.

One of skill in the art would conclude that p16 and p27 were markers negatively associated with apoptosis and terminal differentiation because cells which are rapidly proliferating can not be undergoing apoptosis or terminal differentiation because the activities are mutually exclusive.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to measure p16 and p27 as negative markers of terminal differentiation in the method rendered obvious by the combination of Bacus ('447), and the abstract of Smith and al-Mounhri ,and any of Porter (US 5,498,522) or Los et al (US 6,447,997) or Barbera-Guillem et al (US 5,536,642). One of skill in the art would have been motivated to do so by the teachings of the abstracts of Gillette et al and Emig et al which correlated low levels of p27 with rapidly proliferating breast cells and aberrant expression of p16 with rapidly proliferating breast cells. One of skill in the art would have been motivated to include negative

markers of terminal differentiation to provide a complete pattern of the cell population of the patient's tumor to verify if tumor population reduction or stabilization was occurring as a result of the treatment. The inclusion of only positive markers of apoptosis or terminal differentiation would only provide indices for cells positively stained thereby. In the event that some of the tumor cell population were undergoing apoptosis and some of the tumor cell population were undergoing terminal differentiation, and the remainder of the tumor cell population were undergoing rapid growth, measurement of the markers of apoptosis or terminal differentiation alone or together would not provide a representative measurement for the total cell population.

8. Applicant argues on the bottom of page 4 that important distinctions between the prior art references are being ignored by the examiner. Applicant states that by ignoring the difference between the teachings of Bacus I and the instant claims which require a comparison of two separate samples obtained at separate time the Office action fails to appreciate that in contrast to Bacus I the instant method claims are different. This has been considered but not found persuasive. Applicant is reminded that if the teachings of Bacus I were the same as that of the instant claims, the rejection would have been made under 35 U.S.C. 102 rather than 103. The prior Office action directly addressed this difference between Bacus I and the instant claims, stating

One of skill in the art would always be motivate to extend in vitro methods of treating tumor cells to in vivo methods of treating patients with tumors as long as there was reasonable expectation of success. Thus, although Bacus teaches only a single biopsy sample, said sample is divided into two portions and one is exposed to a therapeutic agent and the other is maintained as a control, the method of Bacus is analogous to the instant method wherein the first sample is the control because the individual with the tumor has not yet been exposed to the therapeutic agent and the second sample is after exposure to the therapeutic agent corresponding to a sample obtained from an individual after exposure to the agent in vivo. There is a direct correspondence with the method of Bacus.

Applicant repeatedly quotes the examiner out of context stating that the examiner said that one of skill in the art "would always" be motivated to extend in vitro methods of treating tumor cells to in vivo methods. This is out of context. The examiner clearly qualified this statement with "as

long as there was reasonable expectation of success". Applicant does not provide arguments of why in the case of the in vitro method of Bacus I, there would be no reasonable expectation of success. The examiner would like to point out that the objective of any in vitro method is the screening of methods and reagents before application to an in vivo method. The examiner contends there is no other motivation for inducing cell death in vitro. The tumor cells growing in culture can be killed by removing them from the culture environment, i.e. discarding them in the waste bin. The only motivation for finding chemical agents which selectively induce cell death of tumor cells in culture is the application of said agents to induce cell death in vivo. The tumor cells in culture are not causing a pathological condition in an individual because they are not responsible for autologous tumor grow within an individual by virtue of growing on a cell culture dish. There is no motivation other than the testing of chemical agents on said cells than the future treatment of an individual suffering from a tumor. Applicant puts the reverse question to the examiner on the top of page 5 and inquires if when presented with an in vitro method, enablement would be sufficient for an in vivo method. The examiner replies that without information regarding the contrary, (i.e. scientific reasoning indicating why there would not be reasonable expectation of success or scientific reasoning supporting undue experimentation) an in vitro method would indeed provide enablement and motivation for an in vitro method. Further, the inclusion of and any of the abstract of Smith and al-Mounhri and any of Porter (US 5,498,522) or Los et al (US 6,447,997) or Barbera-Guillem et al (US 5,536,642) in the instant rejection renders moot applicants objection as to the lack of obviousness of obtaining a biopsy sample after in vivo treatment.

Applicant again argues that it is not whether the differences between the claimed invention and the teachings of the Bacus I reference would themselves have been obvious, but whether the claimed invention as a whole would have been obvious. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicant further argues that the present invention is not drawn to methods for in vivo treatment of an individual with a chemotherapeutic agent but rather to the assessment of the response of an individual to such treatment. Applicant contends that the Office

action improperly focused on whether it would have been obvious on whether to treat individuals with an agent know to be effective for the treatment of cells in culture rather than a method of prognosticating the effectiveness of a therapeutic agent by removing a biopsy sample from an individual before and after the treatment. Applicant contends that because the Office oversimplified the determination of obviousness a prima facie case against the instant invention has failed. This has been considered but not found persuasive. The last active method step in claim 1 requires the determining if a biological marker associated with apoptosis was increased following exposure to the chemotherapeutic agent. Bacus I teaches the

a method for determining the effectiveness of a therapeutic agent in the treatment of cancer by measurement the ability of the therapeutic agent to induce terminal differentiation wherein malignant cells of the cancer over express an oncogene product comprising obtaining from a human having cancer a biopsy comprising viable malignant cells; dividing said biopsy into a first and a second portion; treating the first portion with a compound having specific binding affinity for said oncogene product; maintaining said first and second portions in physiologically acceptable medium for an amount of time sufficient to induce maturation in the viable malignant cells of the first portion; and comparing the percentage of cells in the first portion which exhibit markers of terminal differentiation with the percentage of cells in the second portion which exhibit markers of terminal differentiation, wherein the effectiveness of treatment correlated with the degree of terminal cell differentiation, or alternatively comparing the amount of oncogene product in said first portion with the amount of a oncogene product in said second portion (claims 1 and 10). Bacus teaches that cell proliferation is yet another measure of the extent of terminal cell differentiation, and that a stabilization and reduction of cell populations as compared to untreated control cells indicates substantial terminal differentiation (column 11, lines 53-61).

Clearly the determination of the effectiveness of cancer therapy taught by Bacus I is the same as determining a response to administration of a chemotherapeutic agent to an individual. Note the first sentence of the abstract of Bacus I which states

A method for prognosticating the effectiveness of a chemotherapy using monoclonal antibodies and ligand molecules.

In addition, on column 1, line 63 to column 2, line 19:
In view of the unpredictability of the effect, if any, of an antibody on malignant cells, it has not been possible to determine, prior to starting therapy, whether one or more selected antibodies would be active as anti-tumor agents or to render an accurate prognosis. Heretofore, it has not been possible to determine which antibody preparations, of a selection of monoclonal antibodies (each of which is capable of specifically binding an oncogenic protein) are tumor antagonists, and which are tumor agonists that may undesirably accelerate proliferation of the malignancy. It would be extremely desirable to be able to determine in an in vitro assay method which antibody preparation (or combination of antibodies) having specific affinity for an oncogenic product, and how much thereof, would be predicted to inhibit the proliferation of malignant cells and provide a good prognosis for the patient. It would be very desirable to provide an in vitro method for prognosticating the efficacy[emphasis added] of a proposed therapeutic agent (or combination of agents) and dosage thereof, which method is time- and cost-effective, as well as minimally traumatic to a cancer patient, so that the method may be practically employed in the great variety of cancer cases to be found among different patients.

and on column 2, line 38 to column 3, line 5:
Thus, a method of the present invention entails a method for determining/prognosticating[emphasis added] the effectiveness of a therapeutic agent in the treatment of a cancer wherein malignant cells of the cancer express or overexpress an oncogene product, the method comprising the steps of: (a) obtaining viable malignant cells which express or overexpress at least one oncogene product and dividing the same into first and second portions; (b) treating the first portion comprising viable malignant cells with a sufficient quantity of a composition comprising at least one compound having specific binding affinity for the oncogene product and contacting the second portion with a composition which is devoid of the compound or compounds having specific binding affinity for the oncogene product and incubating the first and second portions in a physiologically acceptable medium for an amount of time sufficient to induce a percentage of the viable malignant cells of said first portion to terminally differentiate; and (c) comparing the percentage of cells in the first portion which exhibit morphological evidence of said terminal differentiation to the percentage of cells in the

second portion which exhibit morphological evidence of terminal differentiation, or, alternatively, comparing the average value across the first portion of a parameter indicative of terminal differentiation with the average value of the parameter across the second portion. The viable malignant cells may be obtained as a tissue biopsy from a patient suffering from a malignancy in which case a therapeutic agent tailored to the patient may be selected. Alternatively, the malignant cells may be those of an established transformed cell line derived from a malignant tissue, in which case the method of the present invention may be used as a general screening assay for selecting anti-cancer therapeutic agents effective against such malignancy.

and on column 2, line 48-57

Thus, the present invention entails methods for selecting anti-cancer therapeutic agents, particularly monoclonal antibodies and ligands and prognosticating [emphasis added]the in vivo response to cancer therapy. A detectable increase in terminal cell differentiation in malignant cells, e.g., from a biopsy treated according to the method of the present invention represents potential effectiveness of the composition in cancer therapy and provides a prognostic measure of the potential effectiveness of the therapy in vivo

and on column 4, lines 20-42

In one of its aspects, the present invention entails a method for determining/prognosticating[emphasis added] the effectiveness of a therapeutic agent in the treatment of a cancer characterized by the expression or overexpression of an oncogene product, the method comprising the steps of: (a) obtaining viable malignant cells which express or overexpress at least one oncogene product and dividing the same into first and second portions; (b) treating the first portion comprising viable malignant cells with a sufficient quantity of a composition comprising at least one compound having specific binding affinity for the oncogene product and contacting the second portion with a composition which is devoid of the compound or compounds having specific binding affinity for the oncogene product and incubating the first and second portions in a physiologically acceptable medium for an amount of time sufficient to induce a percentage of the viable malignant cells of said first portion to terminally differentiate;

and (c) comparing the percentage of cells in the first portion which exhibit morphological evidence of said terminal differentiation maturation to the percentage of cells in the second portion which exhibit morphological evidence of terminal differentiation.

and on column 4, line 62 to column 5 line 38

In cancers characterized by the expression or overexpression of HER-2/neu, the HER-2/neu receptor is characteristically present on the surface membrane of the malignant cells, whereas normal cells and cells which have been induced to terminally differentiate in accordance with the present invention are essentially devoid of HER-2/neu on the surface membrane. Among the indications of terminal cell differentiation are the translocation of the HER-2/neu receptor from the surface membrane to the cytoplasm or perinuclear region of the cell, and a transient increase in the total cellular amount of HER-2/neu. By "translocation of the HER-2/neu receptor" is meant that cells which have been induced to terminally differentiate have substantially reduced amounts of HER-2/neu receptor on their surface membrane and transiently increased amounts of HER-2/neu receptor or a portion thereof present in the cytoplasm or perinuclear region of the cell. Thus, in accordance with methods of the present invention, a prognostic determination [emphasis added] of the effectiveness of a cancer therapy utilizing a selected monoclonal antibody or ligand may be made by maintaining a biopsy of cancerous tissue in the presence and absence of an affinity molecule having such putative therapeutic effect and determining whether the tissue maintained in the presence of the affinity molecule has an increased percentage of cells which exhibit translocation of HER-2/neu or other indications of terminal cell differentiation as compared to the percentage of similarly obtained cells which were maintained in the absence of the affinity molecule, or alternatively whether the tissue maintained in the presence of the affinity molecule has a decreased amount of membrane-bound HER-2/neu or an increased amount of cytoplasmic or total cellular HER-2/neu averaged over a sample of cells compared to the same parameter averaged over a sample of cells which were maintained in the absence of the affinity molecule. The method of the present invention may be employed advantageously to determine the efficacy of an affinity molecule at various concentrations or a combination of affinity molecules, for example, a composition comprising at least two monoclonal antibodies

and/or ligands (at one or more concentrations) which individually are capable of inducing terminal differentiation in such malignant cells.

and on column 11, lines 26-46

Alternatively, indicia of terminal differentiation in cells subject to the method of the present invention include morphological changes in cells which are characteristic of a mature cell type. In cases where the morphological change is dramatic, such as a fundamental qualitative change in the shape or structure of a cell as viewed through a microscope, a determination of the extent of cell differentiation may be made by examining the cells under a microscope and counting the number of cells which exhibit qualitative morphological features associated with terminal cell differentiation. Malignant cells characteristically are compact and spherical, whereas terminally differentiated cells characteristically are flattened, having a cytoplasm which exhibits a delicate lacy appearance. The percentage of cells displaying the latter morphological features may be used to quantify the extent of terminal cell differentiation induced by a putative therapeutic agent in a given portion of biopsy and consequently permit a prognosis [emphasis added]relating to the effect of the putative therapeutic agent in the malignancy sought to be treated.

Bacus I repeatedly teaches prognosis of individuals by comparing the response of a biopsy sample to a chemotherapeutic agent in vitro as evidenced by the above quotes. Applicants arguments regarding treating tumors rather than prognosticating effectiveness of an agent are thus rendered moot.

Applicant argues against the nexus between in vitro methods of treating tumors and in vivo methods of treating tumors, stating that

The Federal Circuit has warned against making. the unwarranted assumption that what has been established in vitro will be effective in vivo. The Court, reversing a finding of obviousness for claims drawn to the in vivo use of a compound in view of published reports of in vitro bactericidal activity thereof noted that "simply because a drug gives positive results in vitro, it does not necessarily follow that there is a reasonable probability of success for therapeutic use of 'that drug in vivo-' In re Gangadharam, 13 U.S.P.Q.Zd 1568, 1 570 (Fed. Cir. 1989) (unpublished). In Gangadaram, the Board had affirmed a finding of obviousness in view of one reference, authored by the applicant because "the teachings of Gangadharam considered as a whole would clearly have led one of ordinary skill in the art to use [the compound] in the treatment of mammals infected with M tuberculosis bacteria or M. intracellulare bacteria (as claimed here) with at least a reasonable expectation of success." Id. at 1568. The Federal Circuit rejected this argument because the use of a general reference of positive results 'in an entirely

different context, in vitro. than which is claimed, and precatory encouraging statements relating to uncertain future investigations and possible results" did not meet the statutory burden of prima facie case of obviousness. Further, the Court stated that the attempt to show that the reference "would have provided to one of ordinary skill in the art a reasonable expectation [of success] fell woefully short of its burden". Id. at 1569. There are numerous other examples where the Board has also come to similar conclusions about in vitro results not being predictive of in vivo efficacy. See, e.g., In re Anderson, 30 U-S.P.Q.2d 1866, 1870 (B.P.A.I. 1993) ("We question whether one skilled in the art would accept appellants" test as predictive of %in vivo? results . . . ."); In re Balzarini, 21 U.S-P-Q.2d 1892 (B.P-A.I. 1991) (While the in vitro testing performed on these anti-viral compounds appears to be useful as a screening tool in order to discriminate which of these anti-viral compounds are candidates for further testing to determine if they possess in vivo utility, the in vitro tests were not predictive of in vivo efficacy); cf Novartis Consumer Health Inc. v. Johnson & Johnson - Merck Consumer PharmaceuticalsCo.,62 U.S.P.Q.2d 1757 (3d Cir. 2002) The acid neutralization capacity ('ANC') [in vitro] does not, however represent an antacid's effectiveness in the human body (ie, 'in vivo'), or its ability to relieve the systems of acid reflux, because other factors -such as rate of gastric emptying, rate of secretion of acid and degree of mixing. between the antacid and gastric contents - all bear on the antacid's efficacy."). And Applicant notes that the citation of the plethora of additional references in support of 'the instant ground of rejection does nothing to increase the evidence that the skilled worker would have had such a reasonable expectation of success (i.e., no evidence whatsoever).

All the above has been considered but not found persuasive. The findings in the court cases presented above do not have the same fact pattern as that of the instant claims. In the findings above, an isolated property of a novel substance in vitro was relied upon for enablement for efficacy in vivo. In the instant case, the substances used in the Bacus I were anti-Her2 antibodies already recognized as of the instant filing date to have therapeutic benefits to cancer patients in need thereof. The in vivo effect of said antibodies has already been demonstrated in clinical trials (for example, Baselga et al, Seminars in Oncology, 1999 Aug, 26 (4 suppl 12), pp. 78-83). There would be no reason to think that there was "no evidence whatsoever" that the monoclonal antibodies and ligands employed by Bacus I (column 3, lines 15-27, lines 43-50) would not have a reasonable expectation of efficacy in vivo. Further the teachings of the abstract of Fornier et al are in regard to the administration of Herceptin, which is humanized antibody directed to the Her-2/neu protein and Taxol in a clinical study. Both Herceptin and Taxol demonstrate anti-tumor efficacy in vivo. The teachings of the abstract of Lebwohl et al are in regard to the combined administration of Herceptin and doxorubicin to patients. Doxorubicin is also known in the art to have anti-tumor efficacy. The point of the rejection was not that an unknown compounds could be screened by the method of Bacus I and prognosticated to have an anti-tumor effect, but that combinations of known anti-tumor drugs, already recognized in the art as having anti-tumor effects, would have a reasonable expectation of success in vivo. Therefore

one of skill in the art would be motivated to try them in vivo and monitor the progress of the patient. Further and any of Porter (US 5,498,522) or Los et al (US 6,447,997) or Barbera-Guillem et al (US 5,536,642) teach the monitoring of treatment efficacy in vivo comprising taking a biopsy sample after treatment with a therapeutic agent.

Applicant has presented excerpts from "Cancer, Principles and Practice of Oncology, 6th Edition" to illustrate examples of agents which were effective in vitro but had numerous side effects in vivo. Upon perusal of the entirety of the 6th Edition, it is noted that chapter 19, entitled "Cancer Drug Development", comprises a table on page 349 which indicates that tumor-cell line based assays is responsible for the identification of many of the current anti-cancer drugs.

Applicant continues to assert that the difference between the cited art and the claimed invention is not one of in vitro versus in vivo exposure of cells (page 10). This has been considered but not found persuasive. For the reasons set forth above, the method of Bacus I differs from the instant method in the dividing of a single biopsy sample and prognostication deduced from the behavior of one part of the sample when exposed to a therapeutic agent. The instant method requires that a sample is taken before treatment, a patient is exposed to a therapeutic agent, and another sample is taken. The only difference is the second sample of the instant invention was exposed in vivo to a chemotherapeutic agent which binds to Her-2 rather than being exposed in vitro as taught by Bacus I. This is quite clear from the discussion above. The examiner does not change this position and maintains that the instant invention was not incorrectly "framed". Further, it would be obvious to take a biopsy sample after treatment with a therapeutic agent as evidence by the teaching of any of and any of Porter (US 5,498,522) or Los et al (US 6,447,997) or Barbera-Guillem et al (US 5,536,642) regarding monitoring the therapeutic efficacy in vivo by the taking of a biopsy sample after the administration of a therapeutic agent to assess the presence of a marker indicative of therapeutic efficacy, as exemplified by the abstract of Smith and al-Mounhri (Biomed Pharmacother, 1998, Vol. 52, pp. 116-121) and any of Porter (US 5,498,522) or Los et al (US 6,447,997) or Barbera-Guillem et al (US 5,536,642).

Applicant argues that the instant invention is concerned with determining whether an individual actually responses to treatment with a chemotherapeutic agent by measuring markers

associated with apoptosis, or terminal differentiation. This is true. However, it would be obvious to one of skill in the art to monitor the patients response to said treatment as evidenced by the abstract Smith and al-Mounhri (Biomed Pharmacother, 1998, Vol. 52, pp. 116-121) and any of Porter (US 5,498,522) or Los et al (US 6,447,997) or Barbera-Guillem et al (US 5,536,642) for the reasons set forth above.

Applicant argues that one of skill in the art would not be motivated to extend in vitro methods of treating tumors to in vivo methods of treating patients. This has been considered but not found at all persuasive. Applicant has provided the teachings of DeVita et al as appendix A to demonstrate that agents which cause apoptosis are counter-indicated in vivo experiments. While some instances of toxic effects are inevitably found on the in vivo level, DeVita (Section 2, pp. 345-356) teaches in that in vitro methods, such as tumor-cell line based screens have "identified many current cancer drugs", as well as "defined agents that cross cell-membranes and withstand the intracellular milieu and define agents with effect on tumor cells and provides the pattern of cellular response" (Table 19, page 349)". Thus, there would be ample motivation to extend an in vitro method of killing tumor cells to an in vivo level.

Applicant argues that the measurement of terminal differentiation as taught by Bacus I is not commensurate with measurement of apoptosis. Applicant is once again reminded that the rejection is under 103 not 102. Applicant asserts that the Office takes the unsupported position that the induction of apoptosis in breast cancer cells as a result of chemotherapy would result in a stabilization and reduction of a cell population which would fall under the definition of "terminal differentiation" as set forth in Bacus I. This is not persuasive. Applicant is ignoring the teachings of Warri et al and the abstract of Wu, in the previous Office action wherein it was stated that

Warri et al teach that methods for treating breast cancer should target the induction of apoptosis to breast cancer cells (abstract, last sentence).

The abstract of Wu teaches that apoptosis is a valuable marker for response in patients having primary or adjuvant chemotherapy for breast cancer. Bacus I is not relied upon for teachings regarding apoptosis as a target for breast cancer treatment, but the teachings of Warri et al and the abstract of Wu are commensurate with the stabilization and reduction of a cell

population as taught by Bacus I. Thus, one of skill in the art would be motivated to combine the teachings of Warri et al and the abstract of Wu with the teachings of Bacus I.

9. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

An obviousness-type double-patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g. In reBerg, 140 F.3d, 1428, 46 USPQ2d 1226 (Fed. Cir. 1998): In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993): In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

10. Claims 1, 2, 5 and 6 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 5,288,477 in view of the abstract of Smith and al-Mounhri (Biomed Pharmacother, 1998, Vol. 52, pp. 116-121) and any of Porter (US 5,498,522) or Los et al (US 6,447,997) or Barbera-Guillem et al (US 5,536,642) for the reasons set forth in section 3 above, because the instant claims 1, 2, 5 and 6 are obvious over claims 1-17 of '477.

11. Claims 1-3, 5 and 6 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 5,288,477 in view of the abstract of Smith and al-Mounhri (Biomed Pharmacother, 1998, Vol. 52, pp. 116-121) and any of Porter (US 5,498,522) or Los et al (US 6,447,997) or Barbera-Guillem et al (US 5,536,642) as applied to claims 1, 2, 5 and 6 above and in further view of the abstract of Vollmer et al (Cancer Research, 1992, Vol. 52, pp. 4642-4648) and the abstract of Dannecker et al (Ann Oncol, 1996, Vol. 7, pp. 391-395) and the abstract of Kopp et al (Cancer Research, 1995, Vol. 55, pp. 4512-4515) for the reasons set forth in section 4 above.

12. Claims 1-6 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 5,288,477 in view of the abstract of Smith and al-Mounhri (Biomed Pharmacother, 1998, Vol. 52, pp. 116-121) and any of Porter (US 5,498,522) or Los et al (US 6,447,997) or Barbera-Guillem et al (US 5,536,642) and the abstract of Vollmer et al (Cancer Research, 1992, Vol. 52, pp. 4642-4648) and the abstract of Dannecker et al (Ann Oncol, 1996, Vol. 7, pp. 391-395) and the abstract of Kopp et al (Cancer Research, 1995, Vol. 55, pp. 4512-4515) as applied to claims 1-3, 5 and 6 above, and in further view of Dash et al (US 5,772,998) for the reasons set forth in section 5 above.

13. All other rejections and objections as set forth or maintained in the previous Office action are withdrawn.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571)272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Karen A. Canella, Ph.D.
11/29/2004

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